

### Remarks

The December 7, 2010 Official Action has been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

The present remarks and amendments are being filed as part of the submission required under 37 C.F.R. §1.114, in connection with the Request for Continued Examination, which is submitted concurrently herewith.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the December 7, 2010 Official Action. Therefore, the initial due date for response was March 7, 2011. Accordingly, a petition for a 2 month extension is presented with this response, which is being filed within the two month extension period.

Claims 1-4, 9, 13, 17-20, 25, and 29 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 4,906,457 in view of Japanese Patent Application JP07010772.

The foregoing rejection constitutes the only ground set forth in the December 7, 2010 Official Action for refusing the present application.

In accordance with the instant amendment, new claims 36-41 have been added. Support for the new claims 36 and 37 can be found throughout the application including, for example, at page 7, lines 220-226). Support for new claims 38-41 can be found throughout the application including, for example, at Example 4. No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the present amendment and the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §103(a) rejection of claims 1-4, 9, 13, 17-20, 25, and 29, as set forth in the December 7, 2010 Official Action, cannot be maintained. This ground of rejection is, therefore, respectfully traversed.

CLAIMS 1-4, 9, 13, 17-20, 25, AND 29 ARE NOT RENDERED  
OBVIOUS BY THE '457 PATENT IN VIEW OF THE '772 APPLICATION

Claims 1-4, 9, 13, 17-20, 25 and 29 have been rejected under 35 U.S.C §103(a) for allegedly being unpatentable over the '457 patent in view of the '772 application. The '457 patent allegedly discloses the topical administration of soybean trypsin inhibitors for reducing the risk of skin cancer caused by sunlight or other ultraviolet radiation. The '772 application allegedly teach that soybean trypsin inhibitors include Kunitz-type soybean trypsin inhibitors. It is the Examiner's position that it would have been obvious to a skilled artisan to combine the above disclosures to arrive at the instantly claimed invention. Applicants continue to respectfully disagree with the Examiner's position for the reasons of record and those set forth below.

At the outset, Applicants note that the Examiner relies heavily on the claims, particularly claim 17, of the '457 patent to establish the instant rejection under 35 U.S.C. §103(a) (see, e.g., pages 3-4 of the instant Official Action). However, it is a well settled premise of patent law that it is improper for an Examiner to rely on the claims of a patent to determine what a patent discloses. Indeed, in In re Benno, 226 U.S.P.Q. 683, 686 (Fed. Cir. 1985), the Federal Circuit stated that the "scope of a patent's claims determines what infringes the patent; **it is no measure of what it discloses**" [emphasis added]. Furthermore, a "patent discloses only that which it describes, whether specifically or in general terms, so as to convey intelligence to one capable of understanding."

Notably, the '457 patent fails to provide any evidence that any of the disclosed protease inhibitors are useful in reducing the risk of skin cancer caused by sunlight or ultraviolet exposure. Indeed, the examples of the '457 patent merely provide sun lotion formulations. Moreover, none of the formulations of the '457 patent comprise a trypsin inhibitor, particularly a Kunitz-type soybean trypsin

inhibitor, as instantly claimed. For example, the formulation of Example 1 provides a lotion comprising the chymotrypsin inhibitor potato inhibitor 1, Example 2 provides a lotion comprising the chymotrypsin inhibitor BBI, and Examples 3 and 4 provide lotions comprising an elastase inhibitor and carboxy-peptidase inhibitor, respectively. The '457 patent is void of any evidence that any of the formulations, let alone a formulation comprising the Kunitz-type soybean trypsin inhibitor, reduce the risk of skin cancer caused by sunlight or ultraviolet exposure.

The '457 patent states at column 1, lines 36-44 that "the protease inhibitors can be applied prospectively to interrupt or reverse the biochemical processes in the skin which are caused by sunlight or ultraviolet exposure and that lead to skin cancer." However, after the '457 patent and before the instant invention, it was the understanding in the art that trypsin inhibitors, particularly Kunitz-type soybean trypsin inhibitors (as instantly claimed), could not inhibit sunlight or ultraviolet radiation induced skin cancer.

Applicants submit herewith Huang et al. (Proc. Natl. Acad. Sci. (1997) 94:11957-11962). Huang et al. teach that "solar UV irradiation is the causal factor for the increasing incidence of human skin carcinomas [and that] the activation of the transcription factor activator protein-1 (AP-1) has been shown to be responsible for the tumor promoter action of UV light" (Abstract). Huang et al. further teach that "induced AP-1 activity is required for tumor promoter-induced transformation" and that "it is generally accepted that ... activation of AP-1 is responsible for the tumor progression action of UV light" (pages 11959 and 11962). Significantly, at page 11959 and Figure 3, Huang et al. demonstrate that while the chymotrypsin inhibitor potato inhibitor I (described in the '457 patent) is able to "markedly block both UVB- or UVC-induced AP-1 transactivation." However, the pre-treatment of epidermal cells with soybean trypsin inhibitor "had no significant inhibitory effect on UV-induced AP-1 activity."

In view of the foregoing, it is evident that the understanding in the art at the time of the instant invention was that chymotrypsin inhibitors such as potato inhibitor I, but not trypsin inhibitors such as Kunitz-type trypsin inhibitors could reduce the risk of skin cancer caused by sunlight or ultraviolet exposure.

At page 4 of the instant Official Action, the Examiner acknowledges that the references previously submitted by the Applicants "do in fact suggest BBIs were the preferred protease inhibitors." However, the Examiner contends that these teachings do not negate the teachings of the '457 patent. Applicants respectfully disagree. The '457 patent states that "preferred types of serine protease inhibitors include the chymotrypsin and trypsin families of protease inhibitors derived from plants, such as from potatoes and soybeans" (columns 1-2). The '457 patent then specifically identifies the soybean-derived BBI family and the potato inhibitor 1 family as appropriate families of inhibitors (column 2). Both of these families are chymotrypsin inhibitors. The specification of the '457 patent is void of any reference to trypsin inhibitors specifically. Indeed, the term "trypsin" is used just once in the '457 patent at the above cited passage. The '457 patent does not specifically teach the use of a Kunitz-type soybean trypsin inhibitor, as instantly claimed. As stated hereinabove, the '457 patent only describes formulations which comprise chymotrypsin inhibitors and not trypsin inhibitors.

Inasmuch as the '457 patent does not teach using the Kunitz-type soybean trypsin inhibitor, there must be some motivation provided in the prior art for a skilled artisan to use the Kunitz-type soybean trypsin inhibitor in methods of reducing the risk of ultraviolet radiation-induced skin cancer, as instantly claimed. The '457 patent is void of any evidence that any protease inhibitor, let alone a Kunitz-type soybean trypsin inhibitor, could be used to reduce the risk of ultraviolet radiation-induced skin cancer. Further, the art

published after the filing of the '457 patent and before the earliest effective filing date of the instant application certainly does not provide a skilled artisan with motivation for using the Kunitz-type soybean trypsin inhibitor to reduce the risk of ultraviolet radiation-induced skin cancer. In contrast, the prior art clearly teaches the skilled artisan to use the chymotrypsin inhibitor BBI and to avoid the Kunitz-type soybean trypsin inhibitor. As explained hereinabove and in previous Official Action response, the following references all clearly teach away from the instantly claimed invention:

1) Huang et al. demonstrate that while chymotrypsin inhibitors are capable of inhibiting the UV-activation of AP-1, which Huang et al. identify as being required for tumor promotion, trypsin inhibitors, such as the soybean trypsin inhibitor, are completely incapable of inhibiting AP-1 activation by ultraviolet radiation.

2) Kennedy (Amer. J. Clin. Ntr. (1998) 68:1406S-1412S; previously submitted) clearly and unequivocally state that "the ability to inhibit carcinogenesis is associated with the ability to inhibit chymotrypsin" (page 1407S). Thus, it was clearly understood by those in the art that only chymotrypsin inhibitors inhibited carcinogenesis.

3) Yavelow et al. (Proc. Natl. Acad. Sci. (1985) 82:5395-5399; previously submitted) state that "other soybean protease inhibitors ... lack the ability to suppress transformation *in vitro*" (page 5395). Yavelow et al. further state that the "Kunitz soybean trypsin inhibitor, which inhibits primarily trypsin, has no effect on radiation-induced transformation" (page 5398; emphasis added).

4) Messina et al. (J. Natl. Cancer Inst. (1991) 83:541-546; previously submitted) state that "comparisons of the pure BBI with an extract of soybeans containing BBI indicate that the activity of the soybean extract could be **directly attributable to BBI**" (page 542; emphasis added).

In view of the foregoing, it is evident that as of the date of the instant invention, the art clearly taught that

the Kunitz-type soybean trypsin inhibitor *cannot* inhibit the ultraviolet activation of AP-1, which is required for tumor promotion; that the ability to inhibit carcinogenesis is associated with the ability to inhibit chymotrypsin (not trypsin); that the Kunitz-type soybean trypsin inhibitor *cannot* inhibit radiation-induced transformation; and that the anti-cancer activity of soybean extract is completely attributable to the chymotrypsin inhibitor BBI. The weight of this evidence clearly would prevent a skilled artisan from using a Kunitz-type soybean trypsin inhibitor in the methods of the '457 patent. Indeed, the '457 patent, at best, only mentions trypsin inhibitors in passing. Further, the '457 patent never specifically exemplifies a trypsin inhibitor, never proposes a specific formulation with a trypsin inhibitor, and fails to provide any evidence or even sound reasoning that a trypsin inhibitor would work in the recited methods. Clearly, the skilled artisan would not have the motivation to use a Kunitz-type soybean trypsin inhibitor to reduce the risk of ultraviolet radiation-induced skin cancer.

At pages 5-6 of the instant Official Action, the Examiner disagrees that the results show an unexpected improvement. Applicants respectfully disagree. At the outset, liposomes are a common carrier that may be used to topically deliver a protein (see, e.g., pages 14-16 of the instant application). Notably, when the treatment is soymilk, such liposomes are unnecessary. As seen in Table 1 and Figure 1 of U.S. Patent Application No. 10/108,248, 100% of mice which received no treatment had tumors by 21 weeks after UVB exposure. When mice were treated with liposomes alone, 96.7% of mice developed tumors by 21 weeks. The treatment of mice with liposomes and BBI - the preferred protease inhibitor in the art, as acknowledged by the Examiner - reduced the number of mice possessing tumors at 21 weeks to 90%. However, surprisingly and unexpectedly, treating mice with the Kunitz-type soybean trypsin inhibitor and liposomes outperformed the preferred BBI as only 80% of mice had tumors at 21 weeks.

The Examiner states at pages 5-6 of the instant Official Action that the "results show the increase in tumor volume caused by liposomes is simply countered by the effect of STI, producing a net change which is not statistically different than no treatment at all." However, Applicants note that the results demonstrate the surprising result that the administration of the Kunitz-type soybean trypsin inhibitor alone was as good, if not superior, to the administration of the "preferred" protease inhibitor BBI. For all of the reasons set forth above, it is evident that there was no teaching or suggestion in the prior art that the Kunitz-type soybean trypsin inhibitor would be effective at reducing the risk of ultraviolet radiation-induced skin cancer. Yet, as demonstrated in Figures 1, 2, and 4 and Table 1 of U.S. Patent Application No. 10/108,248 the Kunitz-type soybean trypsin inhibitor is as effective, if not more effective, at inhibiting tumor formation than BBI. Moreover, Example 4 of the instant application demonstrates that the Kunitz-type soybean trypsin inhibitor, when applied to swine skin, reduced, if not eliminated, DNA damage (thymidine dimer formation) caused by ultraviolet radiation. This finding was neither taught nor suggested by the prior art.

Lastly, at page 6 of the instant Official Action, the Examiner contends that there would be no reason to administer a deactivated/denatured trypsin inhibitor given that it is the purpose to "administer protease inhibitors which have trypsin inhibitor activity." However, as explained hereinabove, the skilled artisan would have neither the motivation nor the expectation of success in using the Kunitz-type soybean trypsin inhibitor at the time of the instant invention. Indeed, the '457 patent provides no data with regard to trypsin inhibitors, exemplifies only chymotrypsin inhibitors, and provides no sound scientific rationale for using trypsin inhibitors. Moreover, the art published in the ten years following the '457 patent unequivocally teaches the skilled artisan that the anti-cancer properties of soy are

contained within the chymotrypsin inhibitor BBI and not trypsin inhibitors.

In view of all of the foregoing, it is clear that the instant rejection of claims 1-4, 9, 13, 17-20, 25, and 29 under 35 U.S.C §103(a) is untenable. Withdrawal of the rejection is respectfully requested.

#### **STATEMENT OF SUBSTANCE OF INTERVIEW**

This Statement of Substance of Interview is being submitted in accordance with §713.04 of the Manual of Patent Examining Procedure to make of record a telephone interview held between Examiner Benjamin Packard and the undersigned on or about April 5, 2011. The Interview Summary Form dated April 7, 2011 indicated that a written reply to the last Official Action must include the Statement of Substance of Interview.

A telephonic interview was held on or about April 5, 2011 between the undersigned and Examiner Packard for the purpose of discussing the references cited in the prior art rejections, particularly the '457 patent, and the features recited in the claims. No definitive agreement with respect to the claims was reached.

This Statement of Substance of Interview is being filed with the reply to the last Official Action in accordance §713.04 of the MPEP.

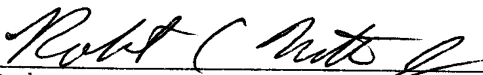
#### **CONCLUSION**

In view of the foregoing remarks, it is respectfully urged that the rejection set forth in the December 7, 2010 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the

Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,  
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